

AD-A189 733

AAMRL-TR-87-071

DTIC FILE COPY ②

*Perceptual and Motor Skills*, 1987, 65, 627-636. © Perceptual and Motor Skills 1987

# STUDY OF NEUROMOTOR REACTION TIMES UNDER THE INFLUENCE OF THYROTROPIN-RELEASING HORMONE

DAN REPPERGER, TOM JENNINGS, JAMES JACOBSON,<sup>1</sup>  
NORMAN MICHEL,<sup>2</sup> CHUCK GOODYEAR,<sup>3</sup> AND LORA HOWELL

*Armstrong Aerospace Medical Research Laboratory, Wright-Patterson AFB, Ohio*

**Summary.**—Neuromotor reaction times (simple, choice, and decision) were measured when Thyrotropin-releasing hormone (TRH) was administered intravenously to nine healthy men in a double-blind study. Measurements were made of simple reaction time, choice reaction time, and decision time for each subject at various intervals over a 54-hr. period. Given the observed inherent interaction of the drug with the long time used (54 hr.), most analyses were conducted across separate time epochs. Injected subjects showed inhibition in the normal improvement of simple reaction time (which occurs with practice), and they reduced the time required to make a decision. Choice reaction time, however, remained unchanged across the drug-nondrug experimental conditions.

Studies of simple reaction time (simple RT) and choice reaction time (choice RT) date back over 100 years (Donders, 1868) and stem from the early interest of man in measuring his ability to respond to a stimulus. The study of reaction times with Thyrotropin-releasing hormone (TRH) is of interest because it is known that TRH improves neuromotor function (Clark & Wither-  
spoon, 1983).

Injections of TRH are frequently used to evaluate suspected thyroid patients. This polypeptide is primarily found in the hypothalamus and, when released, causes the subsequent release of Thyrotropin (TSH)—Thyroid-stimulating Hormone from the pituitary gland. TSH causes the secretion of thyronine ( $T_4$ ) and tri-iodothyronine ( $T_3$ ) from the thyroid gland. The system works in the manner of a classical feedback loop with  $T_3$ , in particular, inhibiting the response to TRH at the pituitary. This chain of events has been reviewed in detail (Burger & Patel, 1977). Snyder and Utiger (1972) discussed the effects of TRH injections on normal subjects, especially with regard to TSH levels in the blood. They found that the TSH response was clearly dependent upon the dosage of TRH, with a maximal response directly related to the TRH dose and inversely related to base levels of thyroid hormone.

Thyrotropin-releasing hormone has been implicated in a myriad of physiologic effects in addition to the production of Thyrotropin-stimulating hormone from the pituitary gland (Burger & Patel, 1977; Snyder & Utiger, 1972).

<sup>1</sup>Wright Patterson Medical Center, Wright-Patterson AFB, Ohio.

<sup>2</sup>Air Force Institute of Technology, Wright-Patterson AFB, Ohio.

<sup>3</sup>Systems Research Laboratory, 2800 Indian Ripple Rd., Dayton, Ohio 45418.

87 12 29 3 59

TRH causes various EEG and autonomic changes (Beale, *et al.*, 1977; Farber, *et al.*, 1981; Wolhuis & De Wied, 1976), increases activity level (Horita & Carino, 1978; Vogel, *et al.*, 1979), and elevates mood (Wilson, *et al.*, 1973). The literature describes conflicting evidence as to whether TRH acts as a stimulant of the central nervous system or possibly as a depressant. Mood elevation does not discriminate between stimulants and depressants of the central nervous system. Until now it appears that the effect of TRH on a simple human performance task has not been investigated within the framework of a device to measure both simple reaction time and decision time. At the Armstrong Aerospace Medical Research Laboratory a simple performance task has been developed using microprocessor based technology that measures both simple and choice reaction times independently (Repperger, *et al.*, 1985) and gives consistent, reproducible measurements. This device has demonstrated (Jacobson, *et al.*, 1986) that reaction times increase with age. Reaction times provide the basis for analysis of any compensatory tracking task which can be broken up into a series of simple stimulus-response actions (Poulton, 1974). The use of these type of performance tests provides a basis for studying performance decrements under stress (Repperger, *et al.*, 1982; Repperger, *et al.*, 1984). In this paper the effect of TRH on different human responses is reported using this sensitive apparatus to measure basic reaction times.

## METHOD

### Apparatus

Fig. 1 illustrates the exterior design of the stimulus-response mechanism. The device has dimensions of approximately 13.3 cm width by 17.2 cm length by 6.4 cm deep. Its faceplate contains two red lights  $L_1$  and  $L_2$  which are the stimuli, and a toggle switch  $S_1$  which is the response indicator. In response to the lighting of a bulb the subject moves the toggle switch toward the light. The device contains a reset mechanism toggle switch  $S_0$  and a green indicator light  $L_0$  for the reset mechanism light. A third toggle switch  $S_2$  is used to set the mode of operation which typically is controlled by the subject.

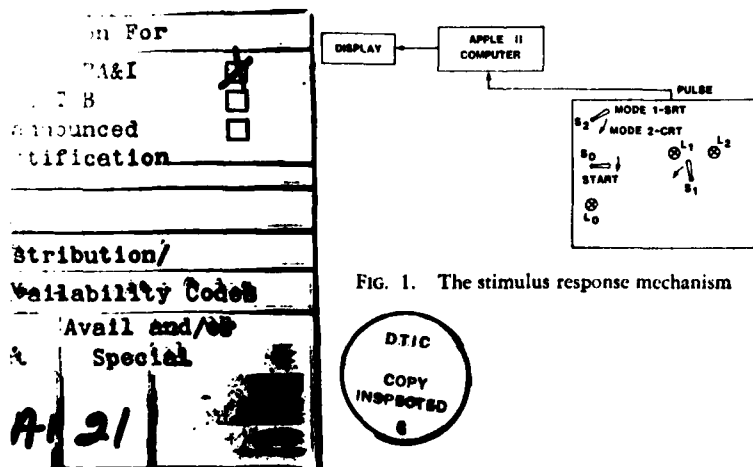


FIG. 1. The stimulus response mechanism

To measure simple reaction time the device is operated in Mode 1. Initially, the green light  $L_0$  is on indicating an inactive state. When the subject resets the toggle switch  $S_0$ , all lights go out. When  $L_1$  lights and the subject responds, the trial is completed. The subject is instructed that in Mode 1 the left light  $L_1$  will always light up, and he also knows that he cannot predict exactly when the light  $L_1$  goes on.

To measure choice reaction time the stimulus-response device is operated in Mode 2. In this mode after  $S_0$  is switched, the indicator light  $L_0$  goes out. After a random period of time  $1 \leq t \leq 6.12$  sec. either  $L_1$  or  $L_2$  will light up in a random sequence. To complete the run the subject must now do two things. First, a decision is made as to which light is on; second, the subject reacts and moves the switch in the direction of the light so the light goes out.

#### *Subjects*

Nine healthy men, members of the United States Air Force, volunteered for the study. Subjects with significant past or present medical history were excluded from the experiment. All subjects were right-handed, and their ages ranged from 23 to 34 yr. They fasted at least 10 hr. prior to the first day of the experiment and did not ingest any caffeine products during the period of the experiment. They trained with the stimulus-response device for approximately one hour on a day prior to the start of the experiment. Subjects were considered to be fully trained after they had completed at least one hundred trials and their scores for three successive replications showed less than a 5% decrease in the score value. Since each subject was run under the nondrug condition (saline) as well as the drug condition (TRH), the learning effects had to be well stabilized before the subject performed a data run. Each subject was instructed to respond quickly, but carefully, so the errors for the choice reaction time task were very small and did not enter into the analysis of these data.

#### *Experimental Procedure*

A heparin lock was inserted into the same arm of a subject for both the TRF and saline injections. The lock was placed in the left arm for four subjects and in the right arm for five subjects. This lock remained in the arm for the first 2 hr. of the experiment and then it was removed. Five hundred micrograms of either Thyrotropin-releasing hormone (TRH) ("Thypinone" Abbott Diagnostic Division) or saline were administered via the heparin lock in a double blind fashion. This TRH dose is routinely used for diagnostic studies in clinical medicine. The mode of operation, simple or choice, and the hand used were selected randomly for each time interval. Fifteen simple and choice reaction time measurements were made with each hand prior to the injection, and at 5, 25, 45, 65, 90 min., 2 hr., 6 hr., 30 hr., and 54 hr. following the injection. Blood samples were taken prior to the injection, and at 20, 40, 60

min., 6 hr., 30 hr., and 54 hr. following the injection. Each subject was tested for one week, randomly assigned, in the control condition (saline) and for one week on the drug condition (TRH). About one week separated the two runs. The results changed with time in the blood analysis from the point of injection of TRH and this is the subject of another paper and is still under review.

#### *Analysis*

This study is concerned with the effects of TRH on human performance over time. One problem, however, with this type of study is the pronounced effects of the drug at a specific time epoch and also the diminished difference between the drug and the nondrug condition after long periods of time. One obvious interaction between the drug and time occurred at the time epoch  $t = 5$  min. Most of the subjects experienced a nauseous feeling at the 5-min. interval after being injected with TRH. To assume this study is still double blind is somewhat contradictory since both the subjects and the experimenter then had an indication which injection was used. This effect manifested itself in plots of simple RT and decision time (cf. Figs. 2 and 3). After the 8-hr. time interval, the effect of the drug should not be that pronounced. To compare a measurement at 54 hr. and 30 hr. to those at 25 min., 45 min., or 65 min. did not seem appropriate so an analysis of variance combining all time periods together was not used.

To adjust for differences in baselines, percent change from baseline was used in the analysis, instead of actual change. The baseline scores refer to the three variables of interest (simple RT, choice RT, and decision time) obtained on the day of the test 20 min. prior to the injection.

TABLE 1  
BASELINE VALUES IN MILLISECONDS (MEAN AND SD)

| Drug   | Sample RT | Choice RT | Decision Time |
|--------|-----------|-----------|---------------|
| Saline | 208±9     | 271±29    | 63±31         |
| TRH    | 197±12    | 259±18    | 62±20         |

One method of analysis would be to use the percent change from baseline for simple RT, choice RT, and decision time as the dependent variables in the analysis of variance. The factors would be subjects, drug (TRH or saline), and time. By considering subjects a random factor (i.e., representing a population), the tests on the factor drug reduce to paired  $t$  tests with data averaged across time periods. There were instances, especially for decision time, when normality could not be assumed. Therefore, the Wilcoxon signed-rank test was used to determine the significance of differences between the drug-

nondrug conditions, since this test is the nonparametric counterpart to the paired *t* test.

Table 1 displays the means and standard deviations of the nine subjects' baseline scores, all times are in milliseconds. Since a large number of tests were performed, there is a possibility of chance significance so the significance of any particular test should be interpreted cautiously.

#### RESULTS

To determine an over-all difference between TRH and saline for simple and choice RT and decision time, the percent changes from baseline were averaged across times for each subject and drug. The time period 5 min. was not included because the injection was close to this performance test. The results of the Wilcoxon signed-rank test are shown in Table 2.

TABLE 2  
MEAN PERCENT CHANGE FROM BASELINE (25 MIN. THROUGH 54 HR.)

| Variable      | Saline      | TRH          | P   |
|---------------|-------------|--------------|-----|
| Simple RT     | -3.7 ± 3.6  | -0.9 ± 2.7   | .07 |
| Choice RT     | -4.6 ± 5.2  | -4.2 ± 4.3   | .91 |
| Decision Time | -1.2 ± 23.9 | -14.0 ± 14.5 | .36 |

One concern with the analysis in Table 2 lies in taking means from 25 min. through 54 hr., for data may be used which involves performance scores before the effects of TRH begin or after the possible effects of TRH have worn off (if the effects exist). To account for this possibility the maximum percent decrease from baseline in the reaction times for any time from 25 min. to 54 hr. was determined for each subject and drug.

TABLE 3  
MEAN OF THE MAX PERCENT DECREASE FROM BASELINE (25 MIN. TO 54 HR.)

| Variable      | Saline       | TRH          | P   |
|---------------|--------------|--------------|-----|
| Simple RT     | -9.4 ± 5.1   | -5.9 ± 2.9   | .25 |
| Choice RT     | -9.9 ± 6.3   | -10.0 ± 4.6  | .82 |
| Decision Time | -19.4 ± 21.6 | -35.3 ± 18.8 | .30 |

As shown in Table 3, the Wilcoxon signed-ranks test was performed for each time individually (5 min. to 54 hr.) with the results shown in Table 4. An analysis of variance of data from all times was not used because there were problems with normality and no desire to have decisions at one time influenced by variability at other times.

From examining the variability among the subjects it is clear that having more subjects is desirable. Although significant differences were difficult to

TABLE 4  
PERCENT CHANGE FROM BASELINE (SIMPLE RT)

| Time Epoch | Simple RT         |                   | Choice RT         |                   | Decision Time      |                    |
|------------|-------------------|-------------------|-------------------|-------------------|--------------------|--------------------|
|            | TRH               | Saline            | TRH               | Saline            | TRH                | Saline             |
| 5 min.     | 3.7               | -0.6              | 0.3               | 0.2               | -7.9               | 13.1               |
| 25 min.    | 1.6               | -2.7              | -1.5              | -2.4              | -12.8              | 0.8                |
| 45 min.    | -0.6              | -1.9              | -1.5              | -2.0              | -2.9               | 3.2                |
| 65 min.    | 0.6               | -0.3              | -2.2              | -1.7              | -10.9              | 0.8                |
| 90 min.    | 0.0               | -1.9              | -3.1              | -3.0              | -13.2              | -0.4               |
| 2 hr.      | 2.3               | -2.6              | -3.4              | -2.8              | -19.1 <sup>c</sup> | 2.6 <sup>c</sup>   |
| 6 hr.      | -3.7              | -5.2 <sup>a</sup> | -6.3 <sup>c</sup> | -6.8 <sup>c</sup> | -14.8 <sup>c</sup> | -1.3 <sup>c</sup>  |
| 30 hr.     | -4.4 <sup>b</sup> | -8.7 <sup>b</sup> | -8.2 <sup>d</sup> | -9.8 <sup>d</sup> | -18.9 <sup>b</sup> | -5.9 <sup>b</sup>  |
| 54 hr.     | -3.2              | -7.3              | -7.4 <sup>c</sup> | -9.4 <sup>c</sup> | -18.4 <sup>c</sup> | -10.9 <sup>c</sup> |

a-i:  $p \leq .04$ .

find between TRH and saline, Figs. 2, 3, and 4 suggest that TRH may slow down simple RT (and thus inhibit learning) but may speed up decision time with the result of no over-all change in choice RT due to the drug. More precise statements to this effect are made below. Tables 5 and 6 illustrate other tests that were performed.

Table 4 indicates that TRH may inhibit learning as suggested by the mean values of simple RT for saline decreasing with time (also see Fig. 2) versus TRH in which mean values of simple RT do not show such large decreases with

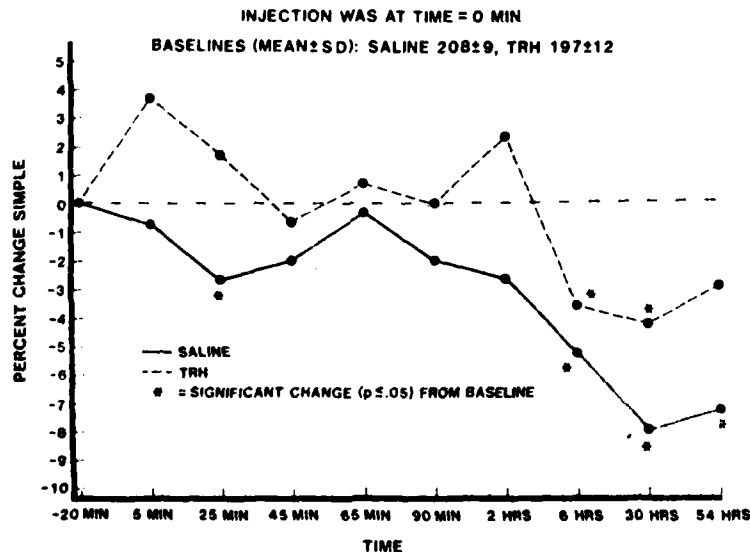


FIG. 2. Plot of the percent change from baseline in simple reaction time vs time

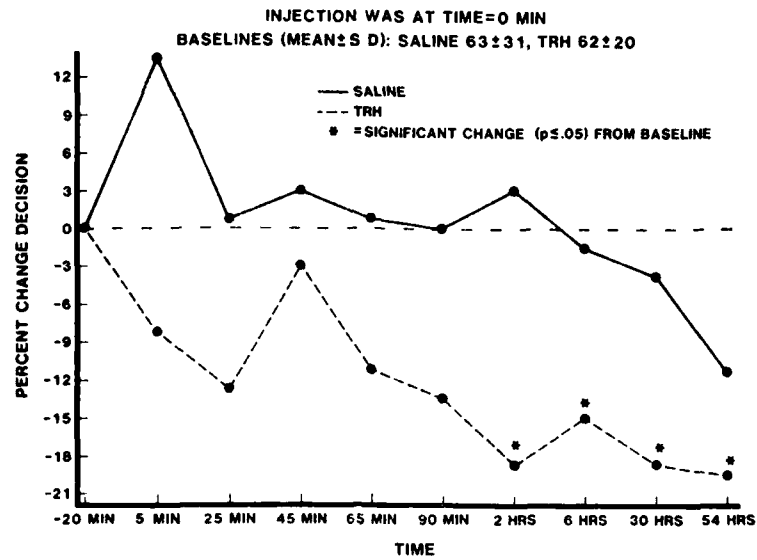


FIG. 3. Plot of the percent change from baseline in decision time vs time

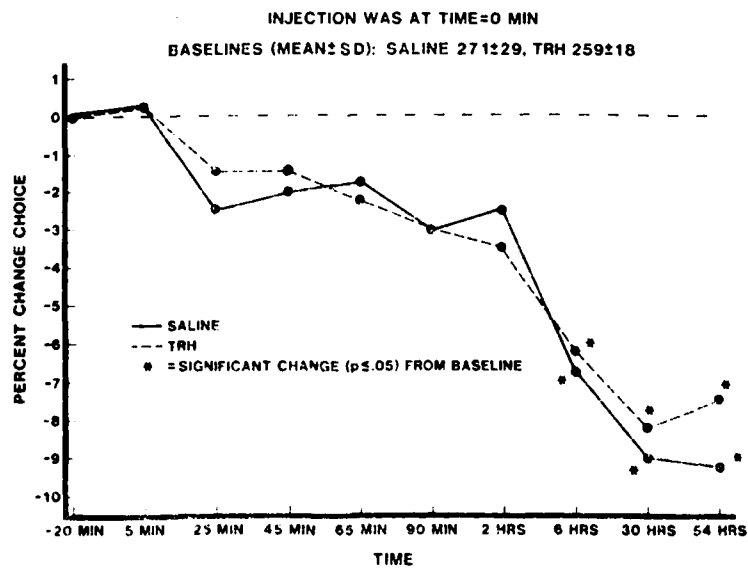


FIG. 4. Plot of the percent change from baseline in choice reaction time vs time

TABLE 5  
HAND WITH HEPARIN LOCK (MEAN  $\pm$  SD WITH TIMES — 20 MIN. TO 54 HR.)

| Variable      | Right        | Left         | P   |
|---------------|--------------|--------------|-----|
| Simple RT     | 200 $\pm$ 10 | 198 $\pm$ 12 | .65 |
| Choice RT     | 255 $\pm$ 17 | 255 $\pm$ 18 | .30 |
| Decision Time | 55 $\pm$ 19  | 57 $\pm$ 21  | .30 |

time. Table 2 shows ( $P = .07$ ) that the mean change in simple RT for TRH tends to be a smaller decrease than in saline, which is suggestive of an inhibition of learning.

In Table 3 the change in mean decision time for TRH was  $-35.3$  msec. versus  $-19.4$  msec. for saline. Obviously practice is still improving decision time in either case. In Table 3, however, all data are averaged over subjects for the time periods 25 min. to 54 hr. In Table 4 this effect is more carefully

TABLE 6  
HEPARIN LOCK (MEAN  $\pm$  SD WITH TIMES — 20 MIN. TO 65 MIN.)

| Variable      | Arm with Lock | Arm without Lock | P   |
|---------------|---------------|------------------|-----|
| Simple RT     | 204 $\pm$ 11  | 201 $\pm$ 9      | .25 |
| Choice RT     | 264 $\pm$ 15  | 259 $\pm$ 21     | .30 |
| Decision Time | 60 $\pm$ 20   | 58 $\pm$ 24      | .36 |

delineated by time periods. TRH has its predominant effect after 90 min. The  $P$  values are significant based on  $P < .1$  for time  $\geq 90$  min. for reduction of decision time for TRH ( $P < .05$  for  $t \geq 2$  hr.), indicating that TRH administration resulted in delayed improvement compared to the control (nondrug) condition.

The last noticeable effect of TRH (Table 2) as compared to saline is the lack of change in choice-reaction time. The mean change in choice RT for saline is  $-4.6$  msec. versus  $-4.2$  msec. for TRH. Fig. 4 clearly illustrates the learning trend in this curve and the small difference between the drug-nondrug conditions.

The mean values indicate TRH results in longer simple RT, shorter decision time, and choice RT about the same. It is noted that since decision time is the difference between choice RT and simple RT, then only two of those three variables are independent. The conclusion is that longer simple RT and shorter decision time are the only independent effects. Fig. 2 illustrates that TRH may inhibit learning. Fig. 3 shows how TRH may reduce decision time, and Fig. 4 illustrates how choice RT remains about the same under the drug-nondrug situation (despite a learning trend in choice RT for both the drug and nondrug conditions).

## DISCUSSION

The goal of this study was to measure objectively the effect of TRH on human reaction time and decision times. TRH may decrease the central processing time (decision time) in healthy men. Previous reports stated that TRH increases alertness, attention, and desire in depressed patients (Itil, *et al.*, 1975; Kastin, *et al.*, 1974; Pecknold & Ban, 1977) and produces an EEG resembling EEGs of subjects administered a psychostimulant compound such as dextro-amphetamine (Itil, *et al.*, 1975). Amphetamines have been reported to decrease both simple (Weiss & Laties, 1962) and choice RT (Adler, *et al.*, 1950). TRH has caused a sense of well-being, increased energy, and mild relaxation lasting up to 8 hr. in normal women (Wilson, *et al.*, 1973) and men (Lipton, *et al.*, 1977). In addition, TRH increases the arousal or activity of various animals and antagonizes the effect of various depressants (Stanton, *et al.*, 1981; Vogel, *et al.*, 1979).

TRH affects cortical neurons but the results appear to be contradictory. TRH has either an inhibitor, excitatory, or no effect on single-cell recordings of sensorimotor cortical neurons in cats depending on the specific neuron tested. TRH may induce a modulating effect on the action of other neurotransmitters (Braitman, *et al.*, 1980; Renaud, *et al.*, 1979). Other results indicate that TRH has only a depressive effect on cortical neurons (Renaud & Martin, 1975).

The simple reaction time test used here consists of a manual response to a light which encompasses many areas of the nervous system including visual and motor reactions. In this study when subjects were injected with TRH they showed slight inhibition in the learning of simple RT, reduced decision time, especially after 90 min., and little difference in choice RT when compared to the saline injection (due to the relative increase in simple RT and decrease in decision time).

## REFERENCES

- ADLER, H. F., BURKHARDT, W. L., IVY, A. C., & ATKINSON, A. J. (1950) Effect of various drugs on psychomotor performance at ground level and at simulated altitudes of 18,000 feet in a low pressure chamber. *Journal of Aviation Medicine*, 1, 221-236.
- BEALE, J. S., WHITE, R. P., & HUANG, S. P. (1977) EEG and blood pressure effects of TRH in rabbits. *Neuropharmacology*, 16, 499-506.
- BRAITMAN, D. J., AUKER, C. R., & CARPENTER, D. O. (1980) Thyrotropin-releasing hormone has multiple actions in cortex. *Brain Research*, 194, 244-248.
- BURGER, H. G., & PATEL, Y. C. (1977) TRH-TSH. In G. M. Besser & L. Martini (Eds.), *Clinical neuroendocrinology*. New York: Academic Press. Pp. 69-86.
- CLARK, M., & WITHERSPOON, D. (1983) Gaining on Gehrig's disease. *Newsweek*, 102 (Aug. 15), 49.
- DONDERS, F. C. Over de Snelheid van psychische Processen. [On the speed of mental processes.] In 'Onderzoekingen gedaan in het Physiologisch Laboratorium der Utrechtsche Hoogeschool, Tweede Reeks, 1868-1869, 2, 92-120. (Published also: *Nederlandsch Archief voor Genees- en Natuurkunde*, 1869, 4, 117-145. In W. G. Koster (Ed.), *Attention and performance II*. *Acta Physiologica*, 1969, 30, 412-431.

- FARBER, J. P., CONNERS, A. F., GISOLFI, C. V., MCCAFFREE, D. R., & SMITH, R. M. (1981) Effects on breathing of putative neurotransmitters in the rostral hypothalamus of the rat. *Brain Research Bulletin*, 6, 13-17.
- HORITA, A., & CARINO, M. A. (1978) Analeptic and antianaleptic effects of naloxone and naltrexone in rabbits. *Life Sciences*, 23, 1681-1686.
- ITIL, T. M., PATTERSON, C. D., POLVAN, N., BIGELOW, A., & BERGEY, B. (1975) Clinical and CNS effects of oral and I.V. thyrotropin-releasing hormone in depressed patients. *Diseases of the Nervous System*, 36, 529-536.
- JACOBSON, J. M., REPPERGER, D. W., GOODYEAR, C., & MICHEL, N. (1986) Effect of directional response variables on eye-hand reaction times and decision time. *Perceptual and Motor Skills*, 62, 195-208.
- KASTIN, A. J., SCHALLY, A. V., EHRENSING, R. H., & BARBEAR, A. (1974) Endocrine and extra-endocrine studies of hypothalamic hormones in man. In K. Lederis & K. E. Cooper (Eds.), *Recent studies of hypothalamic function, International Symposium Calgary 1973*. New York: Karger. Pp. 196-206.
- LIPTON, M. A., PRANGE, A. J., NEMEROFF, C. B., BREESE, G. R., & WILSON, I. C. (1977) Thyrotropin-releasing hormone: central effects in man and animals. In E. Eusdin, D. A. Hamburg, & J. D. Barchas (Eds.), *Proceedings of a Conference on Neuro Regulators and Hypotheses of Psychiatric Disorders Held at Asilomar Conference Center*. New York: Oxford Univer. Press. Pp. 258-266.
- PECKNOLD, J. C., & BAN, T. A. (1977) TRH in depressive illness. *International Pharmacopsychiatry*, 12, 166-173.
- POULTON, E. C. (1974) *Tracking skill and manual control*. New York: Academic Press.
- RENAUD, L. P., BLUME, H. W., PITTMAN, Q. J., LAMOUR, Y., & TAN, A. T. (1979) Thyrotropin-releasing hormone selectively depresses glutamate excitation of cerebral cortical neurons. *Science*, 205, 1275-1276.
- RENAUD, L. P., & MARTIN, J. B. (1975) Thyrotropin-releasing hormone (TRH): depressant action on central neuronal activity. *Brain Research*, 86, 150-154.
- REPPERGER, D. W., JACOBSON, J., MICHEL, N., WALBROEAL, G., & GOODYEAR, C. (1985) Design of a computerized device to measure simple reaction time/decision time for studies on environmental stress. *Journal of Medical Engineering and Technology*, 9, 270-276.
- REPPERGER, D. W., ROGERS, D. B., FRAZIER, J. W., & HUDSON, K. E. (1984) A task difficulty-G stress experiment. *Ergonomics*, 27, 161-176.
- REPPERGER, D. W., ROGERS, D. B., FRAZIER, J. W., & VAN PATTEN, R. E. (1982) A study on human tracking performance in a complex G field experiment. *IEEE Transactions on Systems, Man, and Cybernetics*, SMC-12 (No. 3), 392-401.
- SNYDER, P. J., & UTIGER, R. D. (1972) Response of thyrotropin-releasing hormone (TRH) in normal man. *Journal of Clinical Endocrinology*, 34, 380-385.
- STANTON, T. L., BECKMAN, A. L., & WINOKUR, A. (1981) Thyrotropin-releasing hormone effects in the central nervous system: dependence on arousal state. *Science*, 214, 678-681.
- VOGEL, R. A., COOPER, B. R., BARLOW, T. S., PRANGE, A. J., MUELLER, R. A., & BREESE, G. R. (1979) Effects of thyrotropin-releasing hormone on locomotor activity, operant performance and ingestive behavior. *Journal of Pharmacology & Experimental Therapeutics*, 208, 161-168.
- WEISS, B., & LATIES, V. G. (1962) Enhancement of human performance by caffeine and the amphetamines. *Pharmacology Review*, 14, 1-36.
- WILSON, I. C., PRANGE, A. J., LARA, P. P., ALLTOP, L. B., STIKELATHER, R. A., & LIPTON, M. A. (1973) THR (lopremon): psychobiological responses of normal women. *Archives of General Psychiatry*, 29, 15-21.
- WOLTHUIS, O. L., & DE WIED, D. (1976) The effect of ACTH-analogues on motor behavior and visual evoked responses in rats. *Pharmacology Biochemistry & Behavior*, 4, 273-278.

Accepted September 28, 1987.